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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,072	02/03/2006	Cheol-Min Kim	50413/011001	2285

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EXAMINER	
SHAW, AMANDA MARIE	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/567,072	KIM ET AL.	
	Examiner	Art Unit	
	Amanda Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7,8,10-12 and 14* is/are pending in the application.

4a) Of the above claim(s) *14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3, 7-8, and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply with Sequence Rules*.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on November 25, 2009 has been entered.

Claims 1-3, 7-8, 10-12 and 14 are currently pending.

Claim 14 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on March 6, 2008.

2. It is noted for the record that claim 14 has the wrong status identifier. The status identifier indicates that the claim was "previously presented" however the claim is actually "withdrawn". As per MPEP 714 the current status of all of the claims in an application, including any previously canceled or withdrawn claims, must be given. In order to be responsive to this office action appropriate correction is required.

Sequence Rules

3. This application (see page 18 of the specification) contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below: Patent applications which contain disclosures of nucleotide sequences must contain a paper or compact disc copy of the "Sequence Listing", a computer readable form (CRF) of the "Sequence Listing", and a statement that the "Sequence Listing" content of the paper or compact disc copy and the computer readable copy are the same. In the instant case the sequence of the two QC probes (page 18) are not listed in the "Sequence Listing" as filed by applicants. In order to be responsive to this Office Action applicants are required to amend the paper or compact disc copy of "Sequence Listing" and CRF copy of the "Sequence Listing" to include these sequences. Additionally Applicants should file another statement saying that the "Sequence Listing" content of the paper or compact disc copy and the computer readable copy are the same.

Specification

4. The abstract of the disclosure is objected to because it is over 150 words in length. 37 CFR 1.172 states that "A brief abstract of the technical disclosure in the specification must commence on a separate sheet, preferably following the claims, under the heading "Abstract" or "Abstract of the Disclosure." The sheet or sheets presenting the abstract may not include other parts of the application or other material.

The abstract in an application filed under 35 U.S.C. 111 may not exceed 150 words in length. The purpose of the abstract is to enable the United States Patent and Trademark Office and the public generally to determine quickly from a cursory inspection the nature and gist of the technical disclosure". As such appropriate correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112 1st paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 7-8, and 10-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The analysis used in this Written Description rejection follows the guidelines provided in the Federal Register, Vol. 66, No. 4, January 1, 2001, beginning at page 1099 (referred to in the rejection as "the guidelines").

The guidelines direct one, for each claim, to determine what the claims as a whole cover (p. 1105, 2nd column).

The claims are drawn to oligonucleotides including the nucleotide sequences of point mutations at codons 528, 529, and 514 in domain B and at codons 552, 548, and 555 in domain C of a HBV DNA polymerase gene that induce resistance to lamivudine and/or oligonucleotides including the nucleotide sequences of point mutations at codons 528 and 529 in domain B and at codon 555 in domain C of the HBV DNA polymerase gene that induce resistance to famciclovir.

Here it is noted that the prior art of Liu (Antiviral Chemistry and Chemotherapy Vol 13 pages 143-155) teaches that many different numbering systems for indicating resistance codon positions exist. Liu teaches that based on the entire nucleotide sequences of HBV genomes, HBV has been classified into seven genotypes named A, B, C, D, E, F, and G. Liu teaches that compared to genotype A, alignment of complete genomes from the different genotypes show (1) a 6 nucleotide deletion at the carboxy terminal of the hepatitis B core antigen in genotypes B, C, D, E, F, and G, (2) a 33 nucleotide deletion in the amino-terminal of preS1 in genotype D; and (3) a 3-nucleotide deletion at the amino terminal of genotypes E and G. All three of these variations are located within the ORF of the polymerase gene and thus influence the codon numbering. Liu teaches that with respect to the wild type amino acid sequence there is a “L” at position 528 of genotype A, a “Q” at position 528 of genotypes B, C, and F, and a "F" at position 528 of genotype E and G. Table 2 shows the genotype dependent and independent amino acid numbering for the conserved region B and C of the HBV polymerase RT domain.

The instant claims refer to the point mutations by their amino acid positions however since there are six different HBV genotypes with six different codon numbering schemes the claims do not sufficiently define the point mutations in terms of particular structure and/or function.

Next, the guidelines direct a review of the application to understand how the application provides support for the claimed invention.

The specification (page 12) teaches that there can be a valine to methionine or isoleucine change at codon 552 in domain C of the HBV DNA polymerase gene (M552V or M552I). The specification also teaches a methionine to leucine change at codon 528 in domain B of the HBV polymerase gene. The specification teaches that in addition to codons 552 and 528, codons 514, 529, and 548 are related with resistance to lamivudine and famciclovir. However the specification does not teach the specific amino acid changes that occur at these codons. Additionally the specification does not teach whether the numbering scheme they are using refers to the numbering scheme of HBV genotype A, B, C, D, E, F, or G or some other numbering scheme. As such regarding the mutations at positions 514, 529, 548, and 555 the specific does not sufficiently define the point mutations in terms of particular structure and/or function.

Considering then, the scope of the claims and the teachings of the specification, the guidelines direct one to determine whether there is sufficient written description to inform a skilled artisan that applicant was in possession of the claimed invention as a whole at the time the application was filed. The guidelines direct that such possession may be shown in many ways, including an actual reduction to practice, detailed

drawings or in chemical formulas, and description of sufficient, relevant, identifying characteristics. In addition, for a claim drawn to a genus the requirement may be satisfied by description of a representative number of species, reduction to drawings, or by disclosure of other sufficient, relevant, identifying characteristics.

The claims broadly encompass oligonucleotides including the nucleotide sequences of point mutations at codons 528, 529, and 514 in domain B and at codons 552, 548, and 555 in domain C of the HBV DNA polymerase gene of any of the six known HBV genotypes. Since the claims are so broadly written the specification does not provide sufficient written description to inform one of possession of the invention as a whole.

For these reasons, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the invention as it is broadly claimed and thus the written description requirement has not been satisfied for the claims as they are broadly written. Applicant's attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 'Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

As noted in the MPEP 211.02, " a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation." In the present situation, the structural limitations of the oligonucleotides present on the microarray are able to stand alone and the preamble limitation is not accorded patentable weight. Accordingly, the claim language of "a microarray with target probes for detecting drug resistant HBV on a support" merely sets forth the intended use of the microarray, but does not limit the scope of the claims.

The following rejection has been previously presented

7. Claims 1-3 and 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Fodor (US 2001/0053519 Pub 12/2001).

Regarding Claim 1 Fodor teaches an array comprising all possible nucleic acid sequences of any given length. For example a 10-mer array comprises all possible oligonucleotides containing 10 base positions (Col 17, lines 23-36). While Fodor does

not specifically discuss probes for detecting point mutations at codons 528, 529, and 514 of domain B and at codons 552, 548, and 555 of domain C of the HBV DNA polymerase gene, it is a property of the array taught by Fodor that it would comprise probes capable of detecting these point mutations. In view of the comprising language in the claim the claimed microarray is not limited to probes that only detect these mutations. In the instant case a recitation of a new intended use (i.e. wherein said microarray can be used to detect drug resistant HBV) for an old product (i.e. the microarray of Fodor) does not make a claim to that old product patentable. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art.

Regarding Claim 2 Fodor teaches a microarray on a support wherein the support is a gel (Col 2, lines 34-35).

Regarding Claim 3 Fodor teaches that the probes are oligonucleotides (abstract).

Regarding Claims 7-8 it is inherent that the microarray of Fodor would comprise negative control probes that have been prepared by substituting, inserting, or deleting at least one nucleotide sequence among the nucleotide sequences of the target probes not to be hybridized with a target product.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

As noted in the MPEP 211.02, " a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." In the present situation, the structural limitations of the oligonucleotides present on the microarray are able to stand alone and the preamble limitation is not accorded patentable weight. Accordingly, the claim language of "a microarray with target probes

for detecting drug resistant HBV on a support" merely sets forth the intended use of the microarray, but does not limit the scope of the claims.

The following rejection has been previously presented

9. Claims 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fodor (US 2001/0053519 Pub 12/2001) in view of Kincaid (US 2003/0186310 Filed 4/2003)

The teachings of Fodor are presented above.

Regarding Claim 10 Fodor does not teach a microarray further comprising quality control probes labeled with a fluorescent material having a different excitation/emission wavelength from a fluorescent material used to label the target product. Regarding Claim 11 Fodor does not teach quality control probes that have arbitrary sequences that have at least one nucleotide labeled with a fluorescent material. Regarding Claim 12 Fodor does not teach that the quality control probes are labeled with Cyanine 3 or Cyanine 5.

However Kincaid teaches control probes on a microarray. The control probes can be any known sequence of nucleic acid as long as they do not interfere with the hybridization of the target sample. Kincaid further teaches that the control probes are labeled with a fluorescent material that emits a signal that is distinguishable from any other signal that may be used on the array (para 0016). An example of a label that can be used is CY3 and CY5 (para 0076).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the microarray of Fodor by adding control probes as suggested by Kincaid. The use of control probes were conventional in the field of molecular biology at the time the invention was made and provide the advantage of allowing one to be able to monitor hybridization to determine if the probes on the microarray are working.

The following rejection has been previously presented

10. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vernet (Virus Research 2002) in view of Liu (Antiviral Chemistry and Chemotherapy 2002).

Regarding Claim 1 Vernet teaches that one potential application of DNA Chip technology is in the field of clinical virology and diagnostics, as, for example genotypic resistance tests (page 69). Vernet further teaches that resistance mutations in the genome of HBV have been described in response to antiviral therapies (pages 70).

Regarding Claim 2 Vernet teaches a microarray on a support wherein the support is glass or silica (page 65).

Regarding Claim 3 Vernet teaches that the probes are oligonucleotides (page 65).

Vernet does not disclose probes for detecting point mutations at codons 528, 529, and 514 of domain B and at codons 552, 548, and 555 of domain C of the HBV

DNA polymerase gene.

However Liu teaches that the following mutations in HBV genotype A are associated with drug resistance: in domain B the L528M and F514L amino acid changes and in domain C the M552V/I, A548V, and V/L/M555I amino acid change. Liu also teaches the following mutation in the HBV genotype E and G: T529S amino acid change. Thus mutations at codons 528, 529, and 514 of domain B and at codons 552, 548, and 555 of domain C of the HBV DNA polymerase gene were well known in the art (see Table 2).

While the combined references do not teach probes specific for each of these mutations, it would have been obvious to one of skill in the art to make an array comprising probes to detect these mutations. In the instant case it was well known in the art that allele specific probes could be designed for a specific mutation and that they could be utilized in order to detect that mutation. Designing such probes is considered routine experimentation. Further the parameters and objectives involved in designing these probes were known. Thus the prior art is replete with guidance and information necessary to permit the ordinary artisan to design probes for the detection of the recited point mutations. Further, using the computer programs available an ordinary artisan would have had more than a reasonable expectation of success of making probes for detecting these mutations. Additionally one would have been motivated to put these probes onto a microarray for the benefit of being able to detect the presence or absence of these mutations using microarray technology that overcomes the low sensitivity, the high cost and the long time result of existing tests based on culture and direct or indirect

immunoassay detection (Vernet page 70).

The following rejection has been previously presented

11. Claims 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vernet (Virus Research 2002) in view of Liu (Antiviral Chemistry and Chemotherapy 2002) as applied to claim 1 and in further view of Anderson (US 2003/0040870 Pub 2/2003)

The teachings of Vernet and Liu are presented above.

Regarding Claims 7-8 the combined references do not teach a microarray further comprising negative control probes that have been prepared by substituting, inserting, or deleting at least one nucleotide sequence among the nucleotide sequences of the target probes not to be hybridized with a target product.

However Anderson teaches negative control probes. For single base changes (such as a SNP) one probe was made to be the complement of the wild type sequence, one probe was made to be the complement of the mutated sequence, and one probe was made to be the complement of a different mutation (para 0064). Thus Anderson teaches negative control probes that have been prepared by substituting, inserting, or deleting at least one nucleotide sequence among the nucleotide sequences of the target probes not to be hybridized with a target product.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the microarray of Vernet and Liu by adding negative control probes as suggested by Anderson. The use of control probes

were conventional in the field of molecular biology at the time the invention was made and provide the advantage of allowing one to be able to monitor hybridization to determine if the probes on the microarray are working.

The following rejection has been previously presented

12. Claims 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vernet (Virus Research 2002) in view of Liu (Antiviral Chemistry and Chemotherapy 2002) as applied to claim 1 and in further view of Kincaid (US 2003/0186310 Filed 4/2003).

The teachings of Vernet and Liu are presented above.

The combined references do not teach a microarray further comprising quality control probes labeled with a fluorescent material having a different excitation/emission wavelength from a fluorescent material used to label the target product. Regarding Claim 11 combined references do not teach quality control probes that have arbitrary sequences that have at least one nucleotide labeled with a fluorescent material. Regarding Claim 12 combined references do not teach that the quality control probes is labeled with Cyanine 3 or Cyanine 5.

However Kincaid teaches control probes on a microarray. The control probes can be any known sequence of nucleic acid as long as they do not interfere with the hybridization of the target sample. Kincaid further teaches that the control probes are labeled with a fluorescent material that emits a signal that is distinguishable from any

other signal that may be used on the array (para 0016). An example of a label that can be used is CY3 and CY5 (para 0076).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the microarray of Vernet and Liu by adding control probes as suggested by Kincaid. The use of control probes were conventional in the field of molecular biology at the time the invention was made and provide the advantage of allowing one to be able to monitor hybridization to determine if the probes on the microarray are working.

13. It is noted for the record that the Applicants have argued that Liu does not teach a mutation at codon 529. While the Applicants argument was not found persuasive for the reasons cited in section 16 below, the following are new rejections based on an additional reference Lok (Journal of Clinical Microbiology 2002) which teaches that there is a mutation at codon 529.

The following is a new rejection

14. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lok (Journal of Clinical Microbiology 2002) in view of Liu (Antiviral Chemistry and Chemotherapy 2002).

Regarding Claim 1 Lok teaches a assay designed to detect the presence of different genetic variants of HBV containing mutations located at amino acid positions 528 (180), 552 (204), and 555 (207) in the HBV polymerase protein which confer

resistance to lamivudine (abstract). [Lok teaches that the numbers in parenthesis refer to the proposed numbering scheme by Stuyver et al]. The assay is based on reverse hybridization of amplified HBV DNA fragments with specific nucleotide probes that are immobilized on nitrocellulose strips for each of these mutations (abstract). Additionally Lok teaches that there is a mutation at codon 529 (181) of the HBV polymerase protein (page 3733, col 1). Thus the following mutations in HBV polymerase gene were known in the art at the time of the invention: in domain B the L528M mutation and the mutation at codon 529 and in domain C the M552V/I, A548V, and V/L/M555I mutations (see pages 3730 col 1 and page 3733, col 2).

Regarding Claim 2 Lok teaches a microarray with target probes wherein the support is a membrane (abstract). In the instant case the nitrocellulose strip is being interpreted as a membrane.

Regarding Claim 3 Lok teaches that the probes are oligonucleotides (abstract).

Lok does not disclose the following mutations in the HBV polymerase gene: in domain B the mutation at codon 514 and in domain C the mutation at codon 548.

However Liu teaches that the following mutations in HBV genotype A are associated with drug resistance: in domain B the L528M and F514L mutations and in domain C the M552V/I, A548V, and V/L/M555I mutations. Thus point mutations at codons 528 (180) and 514(166) of domain B and at codons 552 (204), 548 (200), and 555 (207) of domain C of the HBV DNA polymerase gene were well known in the art (see Table 2). Here it is noted that the numbers in parenthesis refer to the proposed numbering scheme by Stuyver et al.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the array of Lok by including probes for detecting the additional drug resistance mutations disclosed by Liu. In the instant case all of the claimed mutations were known in the art at the time of the invention. Additionally it was well known in the art at the time the invention that allele specific probes designed for a mutation could be used in order to detect that mutation. Designing such probes is considered routine experimentation. Further the parameters and objectives involved in designing these probes were known. Thus the prior art is replete with guidance and information necessary to permit the ordinary artisan to design probes for the detection of the recited point mutations. Further, using the computer programs available an ordinary artisan would have had more than a reasonable expectation of success of making probes for detecting these mutations. One of skill in the art would have been motivated to put these probes onto a microarray because array analysis is a rapid and easy to use alternative to sequence analysis for the detection of drug resistance mutations (Lok page 3730). Additionally one of skill in the art would have been motivated to make a probe for the mutation at codon 529 particularly since Lok teaches that the most common reason for discrepant or indeterminate results could be attributed to polymorphism not yet covered by the probes. Specifically Lok teaches that the mutation at codon 529 (181) prohibits both the wild type and mutant probes from annealing at codon 528 (180) (page3733 col 1).

The following is a new rejection

15. Claims 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lok (Journal of Clinical Microbiology 2002) in view of Liu (Antiviral Chemistry and Chemotherapy 2002) as applied to claim 1 and in further view of Anderson (US 2003/0040870 Pub 2/2003)

The teachings of Lok and Liu are presented above.

Regarding Claims 7-8 the combined references does not teach a microarray further comprising negative control probes that have been prepared by substituting, inserting, or deleting at least one nucleotide sequence among the nucleotide sequences of the target probes not to be hybridized with a target product.

However Anderson teaches negative control probes. For single base changes (such as a SNP) one probe was made to be the complement of the wild type sequence, one probe was made to be the complement of the mutated sequence, and one probe was made to be the complement of a different mutation (para 0064). Thus Anderson teaches negative control probes that have been prepared by substituting, inserting, or deleting at least one nucleotide sequence among the nucleotide sequences of the target probes not to be hybridized with a target product.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the microarray of Lok and Liu by adding negative control probes as suggested by Anderson. The use of control probes were conventional in the field of molecular biology at the time the invention was made and provide the advantage of allowing one to be able to monitor hybridization to determine if the probes on the microarray are working.

The following is a new rejection

16. Claims 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lok (Journal of Clinical Microbiology 2002) in view of Liu (Antiviral Chemistry and Chemotherapy 2002) as applied to claim 1 and in further view of Kincaid (US 2003/0186310 Filed 4/2003).

The teachings of Lok and Liu are presented above.

The combined references do not teach a microarray further comprising quality control probes labeled with a fluorescent material having a different excitation/emission wavelength from a fluorescent material used to label the target product. Regarding Claim 11 combined references do not teach quality control probes that have arbitrary sequences that have at least one nucleotide labeled with a fluorescent material. Regarding Claim 12 combined references do not teach that the quality control probes is labeled with Cyanine 3 or Cyanine 5.

However Kincaid teaches control probes on a microarray. The control probes can be any known sequence of nucleic acid as long as they do not interfere with the hybridization of the target sample. Kincaid further teaches that the control probes are labeled with a fluorescent material that emits a signal that is distinguishable from any other signal that may be used on the array (para 0016). An example of a label that can be used is CY3 and CY5 (para 0076).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the microarray of Lok and Liu by adding

control probes as suggested by Kincaid. The use of control probes were conventional in the field of molecular biology at the time the invention was made and provide the advantage of allowing one to be able to monitor hybridization to determine if the probes on the microarray are working.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 7-8, and 10-12 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of copending Application No. 11/860,983 in view of Lok (Journal of Clinical Microbiology 2002) and Liu (Antiviral Chemistry and Chemotherapy 2002). Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are

drawn to oligonucleotides including the nucleotide sequences of point mutations at codons 528 (180), 529 (181), and 514 (166) in domain B and at codons 552 (204), 548 (200), and 555 (207) in domain C of a HBV DNA polymerase gene that induce resistance to lamivudine. Here it is noted that the numbers in parenthesis refer to the numbering system adapted by Stuyver. Similarly the claims of Application 11/860,983 are drawn to oligonucleotides including the nucleotide sequences of the point mutation at codon 528 (180) of domain B and at codons 552 (204) and 555 (207) in domain C of a HBV DNA polymerase gene that are associated to resistance to lamivudine. Additionally both sets of claims require that the oligonucleotides are present on a solid support and both sets of claims require the use of control probes. The instant claims are different from the claims of the copending application because they recite additional mutations. However based on the teachings of Lok the following mutations in HBV polymerase gene were known in the art at the time of the invention: in domain B the L528M mutation and the mutation at codon 529 and in domain C the M552V/I, A548V, and V/L/M555I mutations (see pages 3730 col 1 and page 3733, col 2). Additionally based on the teachings of Liu mutations at codons 528 (180) and 514(166) of domain B and at codons 552 (204), 548 (200), and 555 (207) of domain C of the HBV DNA polymerase gene were well known in the art (see Table 2). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention to make an array including probes for detecting all of the claimed drug resistance mutations. In the instant case all of the claimed mutations were known in the art at the time of the invention. Additionally it was well known in the art at the time the invention that allele

specific probes designed for a mutation could be used in order to detect that mutation. Designing such probes is considered routine experimentation. Further the parameters and objectives involved in designing these probes were known. Thus the prior art is replete with guidance and information necessary to permit the ordinary artisan to design probes for the detection of the recited point mutations. Further, using the computer programs available an ordinary artisan would have had more than a reasonable expectation of success of making probes for detecting these mutations.

This is a provisional obviousness-type double patenting rejection.

Response To Arguments

18. In the response filed November 25, 2009, the Applicants traversed the art rejections.

Regarding the rejection made under 35 USC 102 over Fodor the applicants argue that Fodor does not teach any single array that contains every sequence of any particular length. Rather Fodor teaches a series of arrays designed to systematically include all possible nucleic acid sequences 10 nucleic acids in length. They state that because the total number of 10 mer sequences is so large Fodor constructed four separate chips (Chips A-D, Fig 2-5), each only including a quarter of the total number of possible 10-mer sequences. Further applicants argue that Fodor was not in possession of the claimed microarrays because the genus is too large for one skilled in the art to be able to at once envisage all of the individual species.

This argument has been fully considered but is not persuasive. Fodor teaches an

array comprising 1 X 10^{14} or more nucleic acid probes (para 0003). The phrase "an array" is singular meaning that all the probes are present on a single array. The array comprises a solid support to which are attached all possible nucleic acid sequences of a given length in the entire human genome. For example a 10-mer array comprises all possible oligonucleotides containing 10 base positions. A 10-mer array comprises 4^{10} or 10486576 distinct sequences (Para 0101). The fact that Fodor only exemplifies a set of arrays wherein each array contains all quarter of all of the possible 10 mers is irrelevant because patents are relevant as prior art for all they contain. Disclosed examples and preferred embodiments do not constitute a teaching away from broader disclosures. Further Fodor also contemplates 3 mer arrays which would only have 4000 probes and those arrays could also be used to anticipate the instant claims. As such r the argument that Fodor was not in possession of the claimed microarrays is not persuasive because although it may take a long time one of skill in the could write out the name of each sequence that would be present on a 3 mer or 10 mer array. Further computer programs that were available at the time of the invention would be able to generate a list of all possible combinations. Thus one of skill in the art would be able to at once envisage each sequence.

Regarding the rejection made under 35 USC 103 over Fodor in view of Kincaid the Applicants argue that Kincaid does not make up for the deficiencies of Fodor. Further the Applicants argue that Kincaid discloses that the control probes comprise a sequence of nucleic acids unique to the control probe, whereas the quality control probes of the present invention may have the same sequence as the target probes or

arbitrary sequences as specified in claim 11. In addition they argue that the control probes of Kincaid act as a stilt whereas the control probes of the present claims do not extend the target probes but rather are mixed with the target probes. Finally Applicants state that the control probes of Kincaid also need control specific target material, after hybridization therewith a control signal indicative is interrogated, while the control probes of the present claims do not need any control specific target material and hybridization therewith.

The response to Applicants arguments over Fodor, as set forth above, applies equally to the present grounds of rejection. Kincaid discloses control probes that comprise a sequence of nucleic acids unique to the control probe (abstract). This has been interpreted as meaning that the control probe is different than the target probe. This meets the limitations of claim 11 because claim 11 recites that the controls probes can be arbitrary sequences, meaning that the control probes are comprised of random nucleotides and are different than the target probes which are comprised of specific nucleotides for detecting the point mutations. Regarding the additional arguments that that Kincaid fails to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., probes that are mixed with the target and probes that do not need any control specific target materials and hybridization) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Regarding the rejection made under 35 USC 103 over Vernet in view of Liu the Applicants state that Liu describes codon numbering systems for various genotypes of HBV polymerase which are not identical due to the differing N-termini of each of the genotypes. The Applicants assert that Liu does not teach any mutation at codon 529 of domain B using the A genotype codon numbering system. However Liu does teach a mutation at codon 529 of domain B using the E and G genotype codon numbering system. The Applicants argue that the claims use the same numbering system for codons 528, 514, 552, 548, and 555 as they use for codon 529. This is made clear by the fact the claims specify that the mutations are in "a HBV DNA polymerase gene". According to this numbering system, the codon 529 identified by the Examiner as containing the mutation actually corresponds to codon number 532, which is not specific as including a mutation in the present claims. For these reasons that Applicants state that the combination of these references does not teach or suggest a required element of the present claims: a microarray including a probe having a mutation in codon 529.

This argument has been fully considered but is not persuasive. In the instant it is noted that the prior art of Liu teaches that based on the entire nucleotide sequence of HBV genomes, HBV has been classified into seven genotypes named A, B, C, D, E, F, and G. In the instant case the claims are not limited to a specific HBV genotype, therefore they encompass all of the HBV genotypes. The phrase "a HBV DNA polymerase gene" is being interpreted to mean any HBV DNA polymerase gene whether it is the HBV DNA polymerase gene of genotype A, B, C, D, E, F, or G. Even though the sequences might be different from genotype to genotype they all encode a

variation of a single gene, the HBV DNA polymerase gene. Therefore the fact that Liu teaches a mutation at codon 529 of domain B using the E and G genotype codon numbering system is sufficient to meet this claim limitation. This rejection could be overcome by amending the claims to refer specifically to HBV genotype A, by amending the claims to recite the specific amino acid changes at each codon, or by amending the claims to recite specific SEQ ID Nos. However any amendment must be supported in the specification.

Regarding the additional rejections made under 35 USC 103 the Applicants argue that neither Anderson nor Kincaid make up for the deficiencies of Vernet and Liu.

The response to Applicants arguments over Vernet in view of Liu, as set forth above, applies equally to the present grounds of rejection.

Conclusion

19. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

/Stephen Kapushoc/
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